

### REMARKS

Applicants acknowledge with appreciation the interview granted in Washington by the Examiner on January 19, 1984 to the undersigned, particularly in view of the inclement weather. The preparation given this case by the Examiner is also appreciated. Agreement was reached to advance the prosecution to place the claims in condition for allowance.

Thus, favorable reconsideration of this application is respectfully solicited in view of the interview and this Substitute Amendment.

The instant Amendment is a Substitute Amendment for the Amendment mailed January 18, 1984, but asked to be not entered as per agreement with the Examiner (in a telephone call on January 25, 1984). The "Remarks" portion of that Amendment is incorporated herein by reference (a copy is attached hereto marked Appendix I), supplemented below herein. The claims have been rewritten and represented to facilitate their examination. The numbering of the claims has been made consecutive to the highest number previously presented to avoid duplication.

In the January 18, 1984 Amendment, applicants petitioned for the two necessary extensions of time to February 16, 1984. It is requested that the check attached to said Amendment be applied to the instant Substitute Amendment. Applicants believe that no further fee is due since this Substitute Application is filed within the extension of time already petitioned for. However, the Patent Office is authorized to debit or credit the account of the undersigned, Number 23-0813, for any discrepancy in the amount due.

There are now 29 claims in this application. They have been presented in clear copy and numbered 108-136.

Claims 108 to 127 are product claims; claims 128 to 131 are therapeutic composition claims; claims 132 and 133 are method of use claims and claims 134 to 136 are process claims. All claims - and the claims format - have been simplified. The Examiner agreed that the multiplicity rejection had been overcome. The three claims which were added subsequent to the January 18 proposed Amendment, claims 129, 131 and 136, are drawn even more particularly to more specific and favored aspects of the invention. There is adequate basis in cancelled claims 63 to 81 to support the newly added claims.

Upon review of the claims, some minor changes have been made to improve readability and specificity. The wording of claim 108 has been made to bring it even in closer conformance to 35 USC 112, paragraph 2. Editorially, too, the claim has been improved to refer to the adjective "heparinic" and to "fractions", which is in conformance with the specification, for instance, page 5, last paragraph and continuing on page 6. This language is also in conformance with scientifically accepted terminology. See, please, the Barnett Patent No. 4,351,938 (column 1, line 49 and lines 53-55). Activity is now expressed in units per mg. The claims presented at the interview "appeared to overcome the rejections under 35 USC 112", (as stated in the Interview Record); so do the present ones. Anticoagulation activity has now been referred to as "whole" anticoagulation effect, or as designated in the specification as "overall coagulation"...(at page 6, paragraph 2). The USP assay provides a broad or whole measurement of all anticoagulation effects, i.e. including the

hemorrhagic as well as antithrombic effects. See also the Barnett patent, bridging sentence between columns 6 and 7. Thus, in the claims, the USP activity is clearer contrasted from the selective anti-Xa activity.

As was noted at the interview, the ratio of Yin-Wessler titer to USP titer is a measure of the therapeutic index of the heparinic mucopolysaccharides of the invention. Thus, the ratio of Yin-Wessler titer to USP titer provides a meaningful antithrombotic to hemorrhagic therapeutic index. See, please again the Barnett patent, column 7, lines 5-8 and lines 24-25.

A high ratio of these titers allows for administration of larger doses (wherever prescribed) with less risk of hemorrhaging or for more modest doses with satisfactory antithrombotic effect. It should be noted, that heparin has a Yin-Wessler to USP titer ratio of about 1, thus a very limited therapeutic index. See, Barnett, column 7, line 24. The heparinic mucopolysaccharides of the invention, which have ratios of Yin-Wessler titer to USP titer greater than 1 have thus improved therapeutic value, especially in their improved anti-Xa activity.

The changes in Yin-Wessler to USP ratios in claims 108 and 116, from proposed claims 82 (ratio of 6) and 90 (ratio of 3), reflect an inadvertant switching of values when the former claims were drafted. This is now corrected so that the dependent claim is no longer broader than the claim on which it depends.

As discussed at the interview, a Terminal Disclaimer will be filed in both this application and copending Serial No. 301,611, though the previously made remarks are believed to be

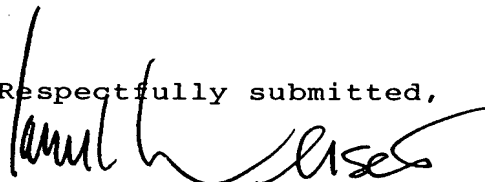
applicable in that regard. It is expected that the Terminal Disclaimers shall be filed within approximately two weeks.

At the interview, the Examiner's suggestion to copy the claims of the Lindhal et al were discussed. Reference is made to pages 11-13 of the Remarks of the previously filed Amendment. The Examiner stated she will reconsider this issue, but did appear to indicate that indeed it could not be seen how applicants herein could copy the claims of that patent. That, it is believed, is the correct disposition of this issue.

A new Exhibit 1 is supplied on letter head of the Academy of Sciences. Thus, the effective dates of this application antedate the publication date of the Proceedings. The certified copies of the French priority documents are of record as of July 13, 1981. There is co-filed herewith verified translations of these priority documents.

It is believed that all open matters have been satisfactorily treated. Accordingly, pursuant to the agreement reached at the interview, this application is in condition for allowance. Such action prior to February 16, 1984 (the end of the next period), is respectfully requested to avoid unnecessary expenses, and will be appreciated.

Respectfully submitted,



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Enclosures:

Appendix 1: Remarks of previous Amendment.

Exhibit 1 : Copy of Letter of the Managing  
Editor Proceedings, National  
Academy of Sciences on  
(letter-head).

Verified Translations (2) of priority  
documents.